ACUTE LEUKEMIA AFTER ALKYLATING-AGENT THERAPY OF OVARIAN CANCER

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Abstract To estimate the leukemogenic potential of alkylating agents, we surveyed 70 institutions using these drugs for the frequency of second cancers in patients with advanced ovarian cancer. Thirteen cases of acute nonlymphocytic leukemia occurred among 5455 patients, as compared to 0.62 cases expected (relative risk = 21.0). All 13 had received alkylating agents. Nine also received radiotherapy. The relative risk for patients given chemotherapy was 36.1 and rose to 171.4 for those surviving for two years (rate = 13.75 per 1000 patients per year). To evaluate the role of therapy versus underlying disease, a historical control of 13,309 patients with ovarian cancer in the National Cancer Institute's End Results Program was analyzed. No excess of leukemia was noted in this group, even among 6596 women receiving radiation. The excess of acute nonlymphocytic leukemia, therefore, appears attributable to alkylating agents, although the effect may be enhanced by exposure to radiation, as previously suggested for Hodgkin's disease. N Engl J Med 297:177-181, 1977)

AN increased risk of leukemia has been reported in patients with multiple myeloma and Hodgkin's disease treated with alkylating agents.[1-3] Although this risk may be directly related to the therapy, longer survival in these diseases may permit expression of an intrinsic predisposition to leukemic transformation.[3] In accumulating case reports, the use of alkylating agents has been suspected in the development of leukemia after treatment for cancers of the ovary,[4-8] breast,[9-11] lung[12,13] and brain,[14] as well as non-neoplastic disorders such as nephritis,[15] rheumatoid arthritis[16] and Wegener's granulomatosis.[17] The effective use of these drugs in advanced ovarian cancer[18] in particular has resulted in a large number of patients at potential risk for long-term sequelae. To evaluate the leukemogenic potential of alkylating agents in ovarian cancer, we made follow-up surveys of two groups of patients: those registered with the End Results Program of the National Cancer Institute, and those identified by a current survey of 70 medical centers using alkylating agents for treatment of this tumor.

METHODS

End Results Program

Data submitted by participants in the End Results Program of the National Cancer Institute were used for this investigation.[19] Included were all women in whom ovarian cancer was diagnosed from 1935 through 1971. Information was available on race, age at diagnosis, initial and subsequent modes of therapy (surgery, radiation, chemotherapy and hormonal therapy), status at annual follow-up examination and subsequent development of other neoplasms. Age and time-specific person-years of survival were tabulated from the diagnosis of ovarian cancer to the diagnosis of a second primary cancer, date of death or closing date of the study (December, 1972), whichever came first. Persons lost to follow-up observation (7 per cent) were included in the analyses and considered at risk of development of a second cancer until the middle of the year in which they were last known to be alive.

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We calculated expected numbers of cancers by applying the age-specific, sex-specific and time-specific incidence rates from the general population to the corresponding person-years of follow-up observation of the patients with ovarian cancer. The rates used were from the Connecticut Tumor Registry.[20] Since 37 per cent of the patients came from Connecticut hospitals, this seemed an appropriate comparison group.

Current Survey

We canvassed members of the Society of Gynecologic Oncologists representing 70 institutions currently involved in the study of alkylating-agent therapy in advanced ovarian carcinoma. We requested information on the number of patients with ovarian cancer treated at each institution from 1970 through 1975, the percentage receiving chemotherapy, the two-year survival of these patients and all cases with second primary neoplasms. Representatives of 51 of these institutions (73 per cent) agreed to participate in the study, contributing a total of 5455 cases. Sixteen of the centers, accounting for 1704 patients, supplied data on two-year survival (24 per cent) and the proportion treated with chemotherapy (80 per cent).

We calculated expected numbers of second cancers in this current survey by applying the age-specific and sex-specific incidence rates obtained in the Third National Cancer Survey, 1969-1971,[21] to the number of person-years at risk. Survival was estimated in two ways. We first applied the age-specific survival experiences of the End Results Programs series to the entire group of patients included in the current survey. This procedure undoubtedly overestimated the person-years of survival since the Program included cases of all stages, whereas the current survey was weighted with patients in more advanced stages as evidenced by the high percentage receiving chemotherapy and the low two-year survival. Secondly, to obtain the person-years of survival for patients receiving chemotherapy (estimated to be 80 per cent of the total on the basis of responses from 16 of the 51 participating centers), the best reported survival experience[22] for advanced ovarian cancer treated with alkylating agents was used. This curve had a two-year survival rate (29 per cent) similar to that of the sample of institutions participating in this study, and provided detailed survival data for longer follow-up periods.

Data on person-years at risk are given by follow-up interval during the period 1970-75, and are not always synonymous with survival since the entry date into the study for each patient was the first time she was treated at the participating institution after 1970.

The strength of association used in both series was the ratio of observed to expected numbers of cases — i.e., the relative risk. Exact 95 per cent confidence intervals were calculated for these estimates under the assumption that the observed number was a Poisson-distributed variable. When the 95 per cent confidence interval does not include 1.0, the estimated relative risk is statistically significant at the 5 per cent level.[23]

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Results

End Results Program

From 1935 through 1972, 13,309 women with ovarian carcinoma of all histologic types and clinical stages were reported to the End Results Program. These patients were followed for 45,903 person-years (mean of 3½ years per person), with 2989 women followed over five years. The average age at diagnosis was 56 years, and the average year of diagnosis and entry into the system was 1958. Of these patients 6596 (49.6 per cent) received radiation as part of their primary treatment. Chemotherapy was used in 2612 (20 per cent of the total), but only 441 were treated during the period covered by the current survey (1970-1975) and, by design of the End Results Program, these patients were followed only until 1972. Information on specific drugs was not stored in the Program file.

A second primary tumor (excluding contralateral ovarian cancer) developed in 364 patients in the total group, as compared with 282 cases expected (relative risk of 1.4 and 95 per cent confidence interval of 1.3 to 1.6). This difference was chiefly due to excesses for cancers of the uterine corpus (relative risk of 3.7 and 95 per cent confidence interval of 3.0 to 4.5) and colon (relative risk of 1.6 and 95 per cent confidence interval of 1.2 to 2.0). Among patients treated with radiation therapy there were 185 second cancers, as compared to 126 expected (relative risk of 1.5 and 95 per cent confidence interval of 1.3 to 1.7); this difference was also largely attributable to excesses for cancers of the uterine corpus and colon.

In five patients leukemia developed as compared to 6.9 expected. Two of these five patients had acute nonlymphocytic leukemia, two had chronic lymphocytic leukemia, and one had chronic granulocytic leukemia. The group receiving radiation therapy accounted for four patients, as compared to 3.0 expected (relative risk of 1.44 and 95 per cent confidence interval of 0.4 to 3.4). No statistically significant trends were found according to interval after diagnosis of ovarian cancer, or to the age or calendar year at diagnosis.

No cases were observed in women treated with chemotherapy. However, the expected value was 0.69 for all 2612 of these women and 0.07 for the 441 women so treated after 1969.

Current Survey

Among the 5455 patients with ovarian cancer identified in the current survey, second primary cancers were reported in 130, as compared with 61.17 expected (relative risk of 2.1 and 95 per cent confidence interval of 1.8 to 2.5). Most of this difference was due to excesses for cancers of the uterine corpus (relative risk of 5.9 and 95 per cent confidence interval of 3.9 to 8.3), colon (relative risk of 2.8 and 95 per cent confidence interval of 1.7 to 4.2) and breast (relative risk of 2.2 and 95 per cent confidence interval of 1.6 to 3.0). In addition, 15 cases of leukemia were reported, as compared with 1.62 expected (relative risk of 9.3 and 95 per cent confidence interval of 5.2 to 15.3).

Table 1. Observed and Expected Cases of Leukemia, Person-Years of Follow-up Observation and Incidence Rates for 5455 Patients with Ovarian Cancer Treated at 51 Institutions between 1970 and 1975.

Datum	Type of Leukemia		
	Acute nonlymphocytic		Other
	total	*>2 yr follow-up period*	
Observed cases	13	12	2
Person-yr	9,167.0	2,485.7	9,167.0
Rate/1000/yr*	1.42	4.83	0.22
Expected cases†	0.62	0.18	1.00
Relative risk‡	21.0	66.7	2.0
95% CI§	11.2–35.9	34.4–116.5	0.2–7.2

*Observed no./person-yr.

†Based on rates prevailing in general population (1969–71).

‡Observed no./expected no.

§95% confidence interval around estimate of relative risk.

As shown in Table 1, the excess of leukemia was due to 13 cases of acute nonlymphocytic leukemia, which was 21 times greater than expected. Twelve of the 13 cases occurred among patients with ovarian cancer who were followed for more than two years. The expected value accrued by this group after the first two years was 0.18 (relative risk of 66.7 and 95 per cent confidence interval of 33.4 to 116.5).

The expected values in Table 1 were based on the End Results Program survival experience of ovarian cancer, which includes all stages and histologic types. To determine the effect of chemotherapy, the best available survival experience for advanced ovarian cancer treated with alkylating agents[22] was applied to 80 per cent of the total group (4324 patients) (Table 2). The expected number of cases of acute nonlymphocytic leukemia in this group was 0.36. All 13 patients with acute nonlymphocytic leukemia were in the chemotherapy group (relative risk of 36.1 and 95 per cent confidence interval of 19.2 to 61.8), and 12 cases occurred in patients followed for two years or longer (relative risk of 171.4 and 95 per cent confidence interval of 88.5 to 299.5).

Table 3 summarizes clinical information available on the 13 patients with acute nonlymphocytic leuke-

Table 2. Observed and Expected Cases of Acute Nonlymphocytic Leukemia, Person-Years of Follow-up Observation and Incidence Rates for 4324 Patients with Ovarian Cancer Treated with Chemotherapy at 51 Institutions between 1970 and 1975.*

Datum	Total	>2 Yr Follow-up Period
Observed cases	13	12
Person-yr	5,385.9	873.0
Rate/1000/yr	2.41	13.75
Expected cases	0.36	0.07
Relative risk	36.1	171.4
95% CI	19.2–61.8	88.5–299.5

*Definitions as in Table 1.

Table 3. Characteristics of Patients with Acute Nonlymphocytic Leukemia in Current Survey.*

Case No.	Type and Duration of Treatment		Radiation Therapy	Latency†	Type of Leukemia	Metastatic Ovarian Cancer at Autopsy
	AA	OC				
	mo		*rads*	*mo*		
1	TT — 46	None	None	52	AML	NA‡
2	UM — 19	5-FU — 19	Pelvis — 4,100	26	AML	NA
3	CTX — 24	None	P-32, pelvis — 4,000	30	AMMoL	No
4	PAM — 30	None	Pelvis — 5,000 Abdomen — 2,000	39	EL	Yes
5	PAM — 22 CTX — 3	5-FU — 20	P-32	44	AML	Yes
6	PAM — 22	None	Pelvis — 2,800	39	AML	No
7	CLR — 24	None	Pelvis — 5,000	44	AML	No
8	CTX — 24	?	?	?	AML	?
9	PAM — 19	None	Pelvis — 5,000 Abdomen — 2,000	36	AML	NA
10	PAM — 8 Hexa — 10	None	Abdominal strip — ?	48	AML	Yes
11	PAM — 17	None	Abdominal strip — ?	31	EL	No
12	CLR — 84	None	None	84	EL	No
13	CLR — 90	None	None	90	AML	No

*AA denotes alkylating agents, OC other chemotherapy, TT thiotepa, UM uracil mustard, CTX cyclophosphamide, PAM phenylalanine mustard, CLR chlorambucil, Hexa hexamethylmelamine, 5-FU 5-fluorouracil, AML acute myelogenous leukemia, AMMoL acute myelomonocytic leukemia & EL erythroleukemia.

†Start of alkylating agents to diagnosis of leukemia.

‡No autopsy.

mia. Nine patients had acute myelogenous leukemia, three erythroleukemia, and one acute myelomonocytic leukemia. All had been treated with alkylating agents; nine (69 per cent) had also received radiation therapy. The primary drugs were phenylalanine mustard (five patients), chlorambucil (three), cyclophosphamide (two), thiotepa (one) and uracil mustard (one). One patient received both phenylalanine mustard and hexamethylmelamine. Two patients were also given 5-fluorouracil. The duration of alkylating-agent therapy ranged from 10 to 90 months (median of 24). Four patients had a "second-look" surgical procedure, resulting in discontinuation of therapy in two.

The interval between onset of chemotherapy and diagnosis of leukemia ranged from 30 to 90 months (median of 41.5). In nine patients, unexplained pancytopenia was the initial manifestation, developing one to 12 months (median of six) before bone-marrow diagnosis of leukemia.

The median survival after the diagnosis of leukemia was 1.5 months; only six patients received antileukemia chemotherapy. Of nine patients autopsied, six had no evidence of ovarian cancer.

Discussion

Although the carcinogenicity of alkylating agents in laboratory animals is well established,[24] the effects in man are poorly defined. The increased risk of leukemia associated with alkylating agents in Hodgkin's disease and multiple myeloma is difficult to interpret, because these underlying diseases may involve the bone marrow and occur with leukemia in the absence of prior chemotherapy.[1,3] In addition, recent improvements in survival for Hodgkin's disease and multiple myeloma might permit expression of leukemia as part of the natural history of these hematopoietic disorders.[3] Ovarian cancer, however, rarely involves the bone marrow, and our survey of patients from the End Results Program indicates no "inherent" excess risk of leukemia in patients with this tumor.

The excess of leukemia in the current survey of patients treated with alkylating agents is unlikely to be explained by selection factors, such as an unrepresentative sample of patients with ovarian cancer or preferential response to the survey by institutions with patients with leukemia. The two-year survival of patients receiving chemotherapy was similar to that previously reported.[18,22] The estimated risk for other second primary tumors, particularly endometrial and colonic cancers, also resembled the pattern seen in the End Results Program survey and other studies of ovarian cancer.[25,26] Furthermore, we know of at least 10 patients with leukemia who were seen at centers that did not respond to the survey (Wharton JC, Cohen CJ: personal communications).

Since the large excess of acute nonlymphocytic leukemia is not likely to be due to chance or selection bias, or to the natural history or cause of ovarian cancer, we consider it prudent to implicate alkylating agents. The leukemogenic potential of these drugs may be related to their capacity to cause chromosomal instability and breakage,[24,27] a feature common to many leukemia-prone states such as constitutional disorders (e.g., Bloom and Fanconi syndromes)[28] or after exposure to ionizing radiation[27] and benzene.[29] Immune mechanisms may also be involved, but acute nonlymphocytic leukemia has not been associated with therapeutic immunosuppression for renal transplantation[30] or with other immunodeficiency states.[31] Although radiotherapy alone was not linked to leuke-

mia in the End Results Program survey or in reported studies of patients with cervical cancer,[32,33] the history of this treatment in nine of the 13 leukemic patients raises the possibility of carcinogenic interactions between radiation and alkylating agents. Similar effects have been demonstrated in laboratory animals[34-37] and suggested in follow-up surveys of Hodgkin's disease[38] and multiple myeloma,[39] but could not be assessed from the data available to us.

Alkylating agents are effective in the treatment of disseminated ovarian cancer, and long-term disease-free survival is possible for as many as 20 per cent of patients who respond.[18] In this study leukemia occurred in only 0.3 per cent of all patients treated at participating institutions. Since untreated advanced ovarian cancer has a median survival of less than 10 months,[40] the potential benefits of therapy clearly outweigh this risk. However, an analysis of the use of these drugs in disorders with better long-term survival rates in untreated patients, such as adjuvant chemotherapy in the early stages of some cancers or as immunosuppressive treatment of nonmalignant disorders, must include an assessment of late effects. Assuming that the rate of acute nonlymphocytic leukemia among those followed for two years or longer (4.83 per 1000 patients per year on the basis of the End Results Program survival or 13.75 per 1000 patients per year on that of a chemotherapy survival curve) is constant over time and due entirely to the alkylating agents, leukemia would be expected to develop in 5 to 10 per cent of a group of patients surviving for 10 years after therapy. This estimated risk may be acceptable with treatment of a disease with a relatively poor prognosis (e.g., breast cancer with axillary-lymph-node involvement) if such therapy results in improved survival. However, the use of these agents in conditions with a more favorable survival rate should take this potential risk into account. Long-term follow-up observation of patients in ongoing adjuvant chemotherapy trials should provide a clearer understanding of the risks and benefits of therapy with alkylating agents. Further studies are also needed to evaluate the carcinogenic effects that may result from interactions between different types of treatment, including radiation and alkylating agents.

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